Analysis of tumor microenvironment identifies features predicting response to checkpoint control inhibitors: A case study comparing the immune microenvironment of uveal melanoma vs skin cutaneous melanoma

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Key findings

- We present a case study to support the idea that gene expression signatures can address a critical unmet need in the immune-oncology space, which is to create a framework for treating tumors that carry less mutation burden combined with poor T-cell infiltration
- Analyzed 476 skin cutaneous melanoma (SKCM) and 80 uveal melanoma (UVM) samples from TCGA. CD8+ T-cell infiltrated tumors were far fewer in UVM <5% compared to SKCM (~30%), the immune microenvironment was qualitatively different in these tumors.

Introduction

The remarkable success of checkpoint control inhibitors in treating a variety of different cancers has necessitated a deeper assessment of the tumor and its microenvironment at a genetic and phenotypic level. Data from recent clinical trials have unequivocally established that the tumor microenvironment significantly impacts the efficacy of immune-oncology drugs.

We have taken a gene expression signature-based approach to qualitatively and quantitatively assess the epithelial, stromal and immune content of tumors from RNA-seq data. The immune cell content of the tumors was further stratified to determine the infiltration pattern of nine different immune cell types including CD8+/CD4+ T-cells, Treg cells, NK cells, dendritic cells, B-cells, myeloid-derived suppressor cells (MDSC) and M1/M2 macrophages in the tumors using gene signatures specific to each immune cell type.

Objectives

1. Investigate the tumor microenvironment using the OncoPept*VAC*™ and OncoPept*TUME*™ solutions.
2. Evaluate tumor neo-epitope burden, and differences in the tumor microenvironment in UVM and SKCM

Methods

- Tumor mutational burden and neo-epitope density of these two tumor types were analyzed by OncoPept*VAC*™.
- Tumor microenvironment analysis was carried out using OncoPept*TUME*™

Figure 1. OncoPept*VAC*™ workflow for the prioritization of T-cell neo-epitopes

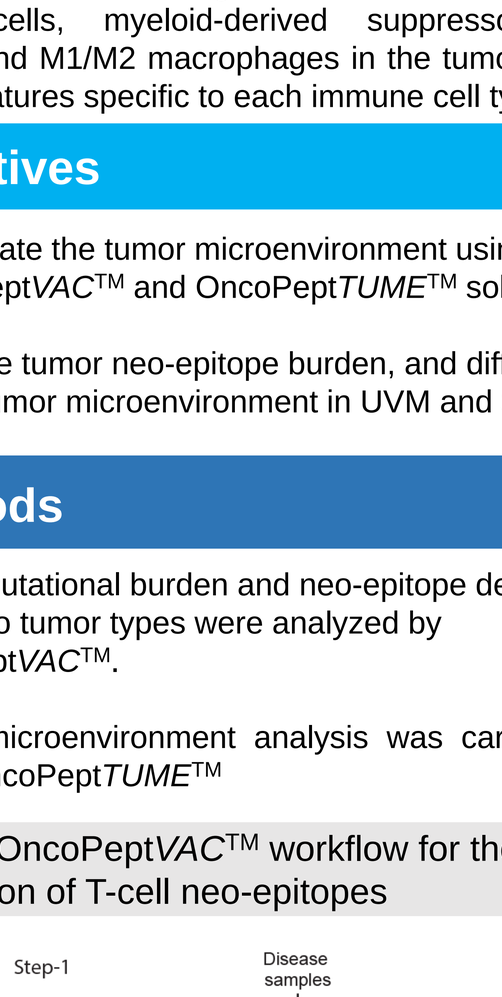


Figure 2. OncoPept*TUME*™ workflow

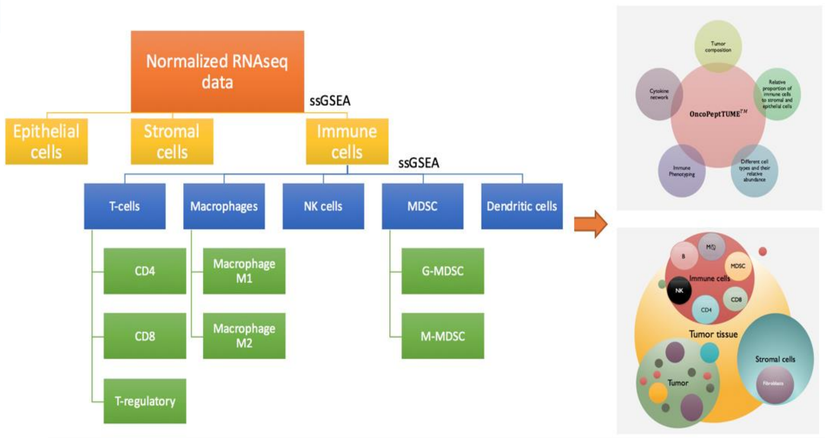
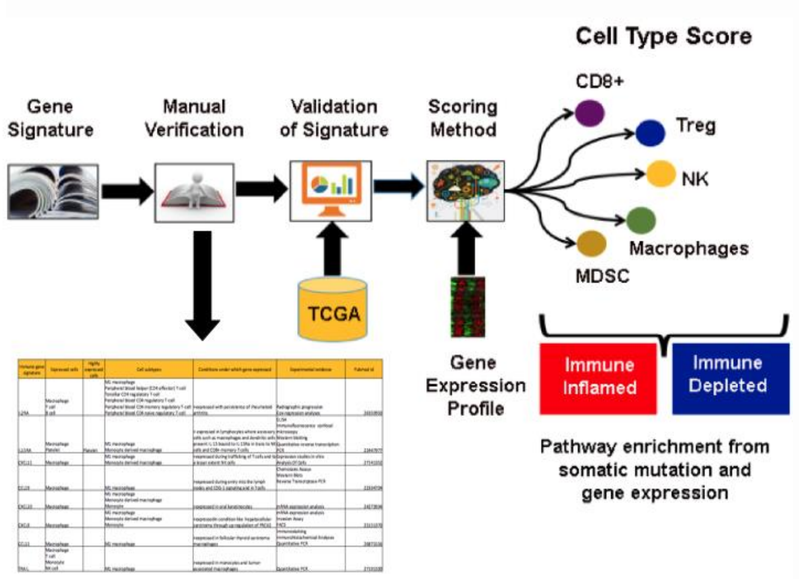


Figure 3. Creation of gene signatures



Results

Figure 4. Epithelial, Stromal and Immune content of 33 cancers from TCGA

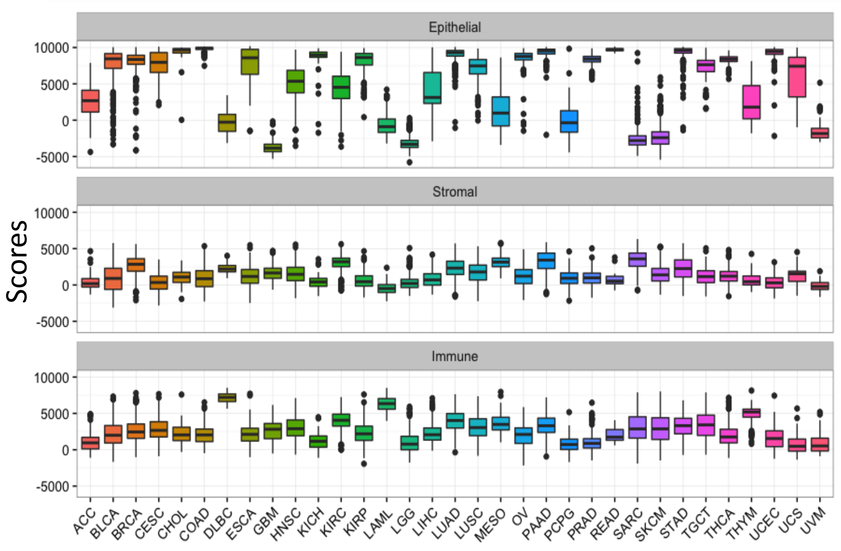


Figure 5. Immune cell infiltration in UVM and SKCM tumors

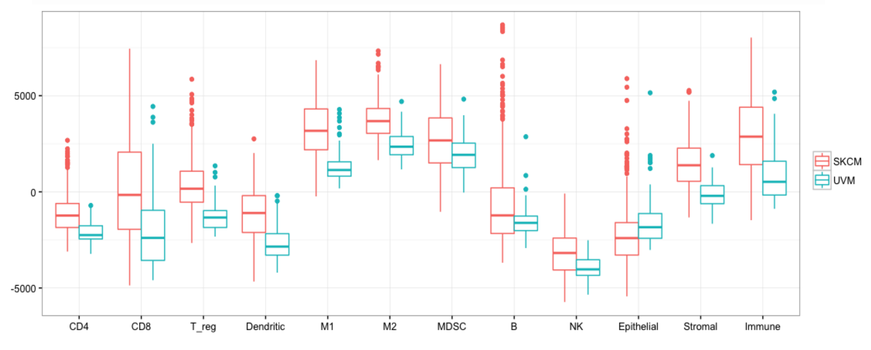
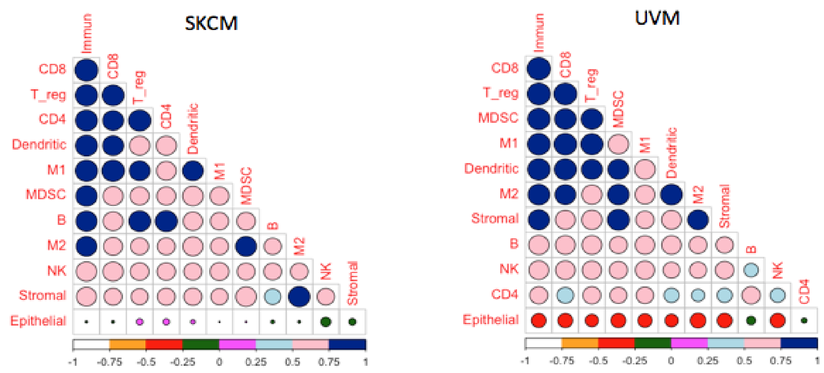


Figure 7. Correlation of different cell types in UVM and SKCM



Immune phenotyping of SKCM and UVM indicates different mechanisms of immune suppression in these two tumor types. In SKCM, CD8 T-cell infiltration is correlated with Treg cells, where as in UVM CD8 T-cell infiltration is correlated with both Treg and MDSC cells

Figure 6. MDSC infiltration in 33 cancers

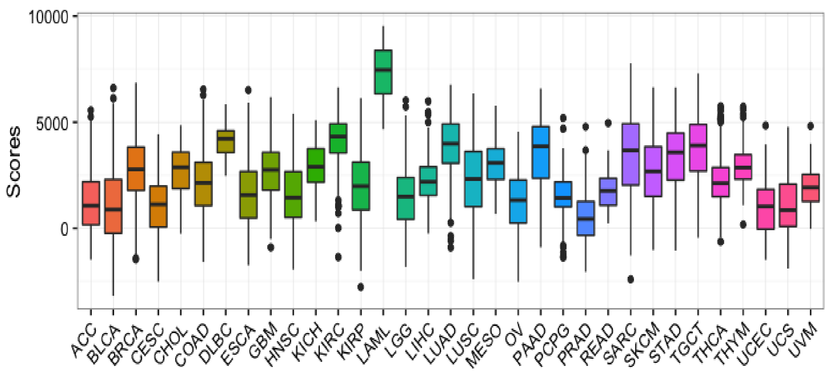
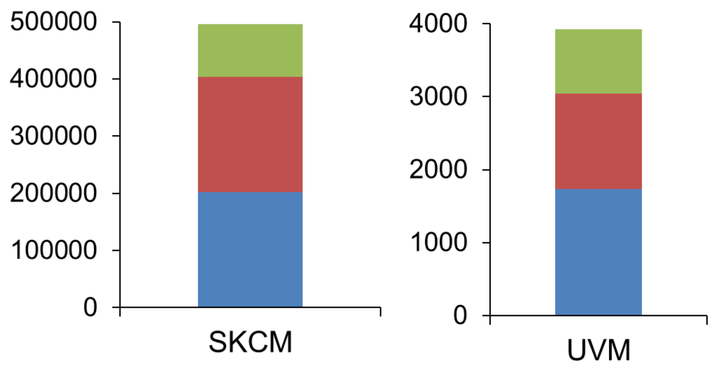


Figure 8. Mutation burden and T-cell neo-epitope content of UVM and SKCM



- Median tumor mutation burden of SKCM is 250 compared to 5 for UVM.
- The neo-epitope burden in SKCM is ~100-fold higher compared to UVM as expected due to higher mutation burden of SKCM
- Ratio of neo-epitope burden to total mutation burden is higher in UVM compared to SKCM (0.46 vs 0.66)

Conclusion

- The UVM melanoma has ~50-fold lower median mutational burden compared to SKCM, which correlates with a lower (<100-fold) T-cell neo-epitope content in these tumors.
- As expected, immune cell infiltration of UVM was significantly lower compared to SKCM and so were the infiltration of different immune cell types, indicating that UVMs are immunologically barren compared to SKCM.
- CD8+ T-cell infiltrated tumors were far fewer in UVM <5% compared to SKCM (~30%)
- By contrast, CD8+ T-cell infiltrated SKCM tumors had significantly lower levels of MDSCs and M2 macrophages and were enriched in dendritic cells, M1 macrophages and Treg cells.
- Significantly, in UVM, the macrophage content was dominated by M2 macrophages (M1:M2, 1:2), whereas in SKCM they were similar.